(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005304 A1

(51) International Patent Classification[7]: C07F 15/00

(21) International Application Number:
PCT/GB2003/002879

(22) International Filing Date: 4 July 2003 (04.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0215526.5 5 July 2002 (05.07.2002) GB

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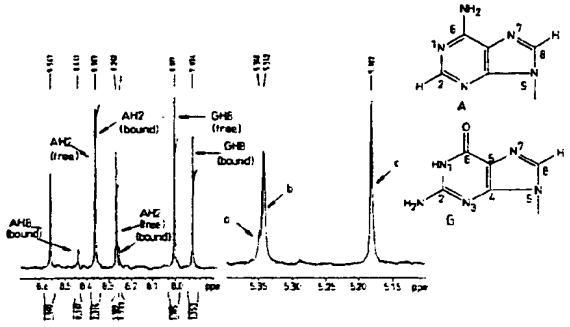
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

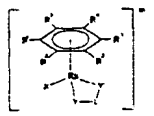
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RUTHENIUM ANTICANCER COMPLEXES





(I)

(57) Abstract: Ruthenium (II) compounds of formula (I) are useful in the treatment and/or prevention of cancer, wherein formula (I) is :

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RUTHENIUM ANTICANCER COMPLEXES

This invention relates to ruthenium(II) compounds, to their use in medicine, particularly for the treatment and/or prevention of cancer, and to a process for their preparation.

Certain ruthenium(II) complexes have been proposed for use in treating cancer. For example, US 4980473 discloses 1,10-phenanthroline complexes of ruthenium(II) and cobalt(III) which are said to be useful for the treatment of tumour cells in a subject.

Some other ruthenium(II) and ruthenium(III) complexes which have been shown to exhibit antitumour activity are mentioned in Guo *et al*, *Inorganica Chimica Acta*, 273 (1998), 1-7, specifically *trans*-$[RuCl_2(DMSO)_4]$, *trans*-$[RuCl_4(imidazole)_2]^-$ and *trans*-$[RuCl_4(indazole)_2]^-$. Clarke *et al* have reviewed the anticancer, and in particular the antimetastatic, activity of ruthenium complexes: *Chem. Rev.*, 1999, **99**, 2511-2533. Also, Sava has reviewed the antimetastatic activity in "Metal Compounds in Cancer Therapy" Ed by S P Fricker, Chapman and Hall, London 1994, p. 65-91.

Dale *et al, Anti-Cancer Drug Design*, (1992), 7, 3-14, describes a metronidazole complex of ruthenium(II) ie, $[(\eta^6\text{-}C_6H_6)RuCl_2(metronidazole)]$ and its effect on DNA and on *E. coli* growth rates. Metronidazole sensitises hypoxic tumour cells to radiation and appears to be an essential element of the complexes of Dale *et al*. There is no indication in Dale *et al* that the complexes would be at all effective in the absence of the metronidazole ligand.

Krämer *et al, Chem Eur J.*, **1996**, 2, No. 12, p. 1518-1526 discloses half sandwich complexes of ruthenium with amino esters.

Bennett *et al*, *Canadian Journal of Chemistry*, (2001), 79, 655-669 discloses certain ruthenium(II) complexes with acetylacetonate ligands.

Oro *et al*, *J Chem Soc*, *Dalton Trans*, (1990), 1463 describes ruthenium(II) complexes containing η^6–p-cymene and acetylacetonate ligands.

WO 01/30790 discloses ruthenium(II) compounds and their use as anticancer agents. The compounds have neutral N-donor ligands and the resulting ruthenium complex is generally positively charged.

WO 02/02572 also discloses ruthenium(II) compounds that have activity against cancer cell lines. Again, the complexes are generally positively-charged. Complexes are disclosed containing a bidentate ligand which is a neutral diamine ligand.

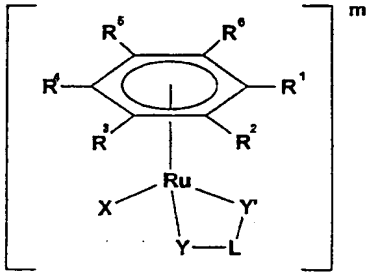
Chen *et al*, *J. Am. Chem. Soc.*, volume 124, no 12, 3064, (2002), describes the mechanism of binding of ruthenium complexes to guanine bases. The binding model requires NH bonds from a diamino ligand to be present in the complex for hydrogen bonding to the guanine base. Similarly, Morris et al, *J. Med. Chem.*, volume 44, 3616-3621, (2001), describes the selectivity of ruthenium(II) complexes for binding to guanine bases.

There exists a need for novel anti-cancer compounds which can be used as alternatives to the compounds which are currently available.

Furthermore, there exists a need for compounds which are capable of binding to different DNA bases. Binding to different DNA bases can provide a compound that exhibits increased activity to drug-resistant tumour cells.

The present invention provides a novel class of ruthenium(II) complexes having anti-tumour activity.

According to the present invention, there is provided a ruthenium(II) compound of formula (I):



(I)

wherein: R^1, R^2, R^3, R^4, R^5 and R^6 independently represent H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, halo, CO_2R^7, $CONR^8R^9$, COR^{10}, SO_3G, $SO_2N\ R^{11}R^{12}$, aryloxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-N=N-R^{13}$, $NR^{14}R^{15}$, aryl or aralkyl, which latter two groups are optionally substituted on the aromatic ring by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aryl, aralkyl, halo, CO_2R^{7a}, $CONR^{8a}R^{9a}$, COR^{10a}, SO_3G', $SO_2NR^{11a}R^{12a}$, aryloxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-N=N-R^{13a}$, $NR^{14a}R^{15a}$, or R^1 and R^2 together with the ring to which they are bound represent a saturated or unsaturated carbocyclic or heterocyclic group containing up to three 3- to 8- membered carbocyclic or heterocyclic rings, wherein each carbocyclic or heterocyclic ring may be fused to one or more other carbocyclic or heterocyclic rings, and wherein each of the rings may be optionally substituted by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-

C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, COR^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, $SO_2NR^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ or (C_1-C_6)alkoxy;

R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and R^{15b} are independently selected from H, (C_1-C_6)alkyl, aryl or aralkyl;

X is a neutral or negatively charged O-, N- or S- donor ligand or halo;

G and G' are independently selected from alkali metals (eg, sodium or potassium), aryl, aralkyl and (C_1-C_6) alkyl;

Y-L-Y' is a bidentate ligand bearing an overall negative charge with a proportion of the charge on both Y and Y', Y and Y' are independently selected from O, S or NR^{16}, wherein R^{16} is H, (C_1-C_6)alkyl, aryl or aralkyl, and L is a group linking Y and Y' and comprises one or more groups selected from (C_1-C_6)alkylene, (C_1-C_6)alkenylene, (C_1-C_6)alkynylene, arylene, aralkylene, alkarylene, each of said latter six groups being optionally substituted, ferrocenylene, Se, Se-Se, S-S, N=N and C=O;

m is –1, 0 or +1 and the compound comprises a counterion when m is –1 or +1;

the compound of formula (I) optionally being in the form of a dimer in which two L groups are linked either directly or through a group comprising one or more of (C_1-C_6)alkylene, (C_1-C_6)alkenylene, arylene, aralkylene, alkarylene, Se, Se-Se, S-S, N=N and C=O or in which L bears two Y groups and two Y' groups;

with the proviso that:

when Y-L-Y' is $(CH_3C(O)CHC(O)CH_3)^-$, X is halo or an N-donor ligand, R^1, R^2, R^3, R^4, R^5 and R^6 together with the ring to which they are bound do not represent 4-isopropyl-1-methylbenzene;

when Y-L-Y' is $(CH_3C(O)CHC(O)CH_3)^-$ and X is chloro, $(CH_3)_2SO$, CH_3CN, pyridine or $(CH_3C(O)CHC(O)CH_3)^-$: R^1, R^2, R^3, R^4, R^5 and R^6 are not all H or all methyl; R^1, R^3 and R^5 are not all H when R^2, R^4 and R^6 are all methyl; and R^2, R^4 and R^6 are not all H when R^1, R^3 and R^5 are all methyl; and

when Y-L-Y' is $(CF_3C(O)CHC(O)CF_3)^-$ and X is chloro, R^1, R^2, R^3, R^4, R^5 and R^6 are not all H or all methyl; R^1, R^3 and R^5 are not all H when R^2, R^4 and R^6 are all methyl; and R^2, R^4 and R^6 are not all H when R^1, R^3 and R^5 are all methyl.

The compounds of the invention may be in the form of pharmaceutically acceptable salts, solvates and/or prodrugs. Prodrugs are variants of the compounds of the invention which can be converted to compounds of formula (I) *in vivo*.

The compounds of formula (I) may have one or more chiral centres. When the compounds of formula (I) have one or more chiral centres, they may be in the form of one enantiomer, may be enriched in one enantiomer or may be a racemic mixture.

The term "alkyl" as used herein includes C_1 to C_6 alkyl groups which may be branched or unbranched and may be open chain or, when they are C_3 to C_6 groups, cyclic. Unbranched open chain alkyl groups include, for example, methyl, ethyl, propyl, butyl, pentyl and hexyl. Branched open chain alkyl groups include, for example, 2-propyl, 2-butyl and 2-(2-methyl)propyl. Cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The alkyl groups in the compounds of the invention may optionally be substituted. Substituents include one or more further unsubstituted alkyl groups and/or one or more further substituents, such as, for example, cyano, nitro, $-CO_2(C_1-C_6)$alkyl, halo, thiol (SH), thioether (eg, $S-(C_1-C_6)$alkyl) and sulfonate. The term "alkoxy" means –O-alkyl. The term "alkylthio" means –S-alkyl.

The terms "hydroxy(C_1-C_6)alkyl" and "amino(C_1-C_6)alkyl" refer to alkyl groups, as defined above, substituted with one or more hydroxyl (OH) or amino (NH_2) groups, respectively.

The terms "alkenyl" and "alkynyl" are defined similarly to the term "alkyl" but refer to groups that contain from 2 to 6 carbon atoms and include one or more carbon-carbon double bonds or one or more carbon-carbon triple bonds, respectively. Alkenyl and alkynyl groups may be optionally substituted in the same way as alkyl groups. Examples of alkenyl groups are ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1,4- butadienyl, cyclohexenyl and cyclohexadienyl.

The term "alkylene" is defined similarly to the definition of the term "alkyl" but includes C_2 to C_6 groups and represents a divalent species with radicals separated by two or more (eg, from two to six) carbon atoms linked in a chain. Preferably, the alkylene groups are straight chain groups. Alkylene groups are optionally substituted in the alkylene chain, preferably with one or more phenylene (eg, 1-4-phenylene) and/or -$CONR^{1x}$- groups and/or -NR^{2x}- groups, where R^{1x} and R^{2x} independently represent H, alkyl, aryl or aralkyl. Preferably, R^{1x} and R^{2x} are H or C_1 to C_3 alkyl. The terms "alkenylene" and "alkynylene" are defined similarly and refer to divalent radicals containing one or more carbon-carbon double bonds or one or more carbon-carbon triple bonds, respectively.

The term "aryl" as used herein includes aromatic carbocyclic rings such as phenyl, naphthyl and anthracenyl and heterocyclic rings such as pyridyl, imidazolyl, pyrrolyl and furanyl. Aryl groups may optionally be substituted with one or more substituents including, for example, (C_1-C_6)alkyl, cyano, nitro, hydroxyl, halo(C_1-C_6)alkyl, -CO_2(C_1-C_6)alkyl, halo, thiol (SH), thioether (eg, S-(C_1-C_6)alkyl) and sulfonate (SO_3H). The term "aryloxy" means –O-aryl.

The term "heterocyclic ring" refers to a 3-, 4-, 5-, 6-, -7, or 8- (preferably 5-, 6- or 7-) membered saturated or unsaturated ring, which may be aromatic or non-aromatic, containing from one to three heteroatoms independently selected from N,O and S, eg, indole.

The term "arylene" refers to a divalent radical comprising an aromatic carbocyclic or heterocyclic ring in which the radicals are present at different positions on the ring. An example of an arylene group is 1,4-phenylene.

The term "aralkyl" means alkyl substituted with aryl eg, benzyl. The term "alkaryl" means aryl substituted with alkyl eg, methylphenyl.

The term "aralkylene" refers to a divalent radical that can be derived from an aralkyl group eg, 1-methylene-4-phenyl. Each of the two radicals may be present on the aryl ring or on the alkyl group or one of the radicals may be present on the alkyl group and the other radical present on the aryl ring. The term "alkarylene" is defined similarly.

The term ferrocenylene refers to a diradical derived from ferrocene ($FeCp_2$). Each radical may be present on the same ring or on different rings.

The term "halo" means a halogen radical selected from fluoro, chloro, bromo and iodo. Chloro is particularly preferred. When X is halo in formula (I), it will be appreciated that X may be thought of as having at least some of the character of a negatively charged ion rather than being covalently bonded to the ruthenium atom. Indeed, all ligands X may have some ionic as well as some covalent character.

The term "haloalkyl" means alkyl substituted with one or more halo groups eg, trifluoromethyl.

In the compounds of the invention, R^1 and R^2 together with the ring to which they are bound in compounds of formula (I) may represent an *ortho-* or *peri-* fused carbocyclic or heterocyclic ring system. R^1 and R^2 together with the ring to which they are bound may, for example, represent a wholly carbocyclic fused ring system such as a ring system containing 2 or 3 fused carbocyclic rings eg, optionally substituted, optionally hydrogenated naphthalene or anthracene. Thus, R^1 and R^2 together with the ring to which they are bound in compounds of formula (I) may represent a fused tricyclic ring such as anthracene or a mono, di, tri, tetra or higher hydrogenated derivative of anthracene. For example, R^1 and R^2 together with the ring to which they are bound in formula (I) may represent anthracene, 1, 4-dihydroanthracene or 1, 4, 9, 10-tetrahydroanthracene. Examples of R^1 and R^2 together with the ring to which they are bound in compounds of formula (I) representing heterocyclic ring systems include those compounds in which R^1 and R^2 together with the ring to which they are bound represent 2,3-benzofuran, indole or benzo[b]thiophene.

Preferably, R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from H, (C_1-C_6)alkyl and phenyl or R^1 and R^2 together with the ring to which they are bound represent anthracene or a hydrogenated derivative of anthracene, said phenyl and anthracene or a hydrogenated derivative of anthracene group being optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, phenyl, benzyl, halo, carboxyl, CO_2(C_1-C_6)alkyl, $CONH_2$, COH, CO(C_1-C_6)alkyl, SO_3H, SO_2NH_2, phenoxy, (C_1-C_6)alkylthio, NH_2 or (C_1-C_6)alkoxy. Most preferably, one of R^1, R^2, R^3, R^4, R^5 and R^6 is phenyl and the other groups are all H, or one or two of R^1, R^2, R^3, R^4, R^5 and R^6 is or are (C_1-

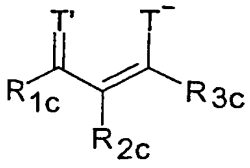
C_6)alkyl and the other groups are H, or R^1 and R^2 together with the ring to which they are bound represent anthracene or a hydrogenated derivative of anthracene.

It can be desirable for the compounds of the invention to be uncharged since this may assist the transport of the compounds in *in vivo* systems and thus their anticancer cytotoxic activity. Therefore, in formula (I), it is preferred that m is 0. When m is +1 or −1, the compounds of formula (I) comprise a counterion. Suitable counterions include non-nucleophilic ions such as, for example, PF_6^- and BF_4^-.

In compounds of formula (I), X is a neutral or negatively charged O-, N- or S-donor ligand or halo. Suitable ligands include, for example, H_2O, di((C_1-C_6)alkyl)S(O), (C_1-C_6)alkylCO_2^- or di((C_1-C_6)alkyl)C=O. Other ligands include, for example, N-donor nitrile ligands (eg, compounds of formula (C_1-C_6)alkylCN) and N-donor pyridine ligands, optionally substituted at one or more of the carbon rings of the pyridine ring eg, by (C_1-C_6)alkyl or halo. Other suitable ligands are (C_1-C_6)alkyl primary amines such as methylamine and ethylamine. Preferably, X is halo or CH_3CN, most preferably, X is chloro.

Y-L-Y' is a bidentate ligand. The ligand has an overall negative charge ie, the ligand would bear a negative charge when not present in the complexes of the invention. The ligand may bear a single negative charge or may have more than one negative charge eg, by being a dianion. Preferably, Y-L-Y' has a single or double negative charge. The charge may be distributed throughout the ligand but a proportion of the charge is present on both Y and Y'. The charge may be due to the formation of an anion by deprotonation at Y and/or Y' or by delocalisation of the charge from Y to Y' or *vice versa*. Preferably, there is delocalisation of the charge from Y to Y' or from Y' to Y by conjugation of electrons through L. L may comprise one or more groups, for

example L can comprise an alkylene group having a CO group at each end of the alkylene chain. Preferably, Y-L-Y' is selected from ligands of formulae



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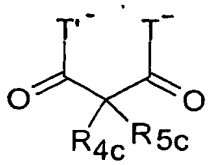

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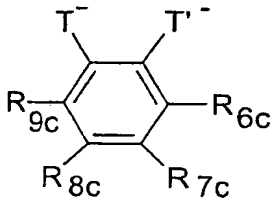

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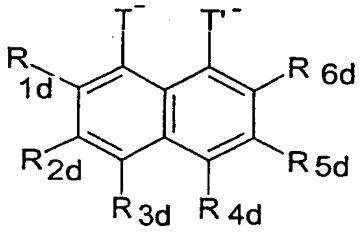
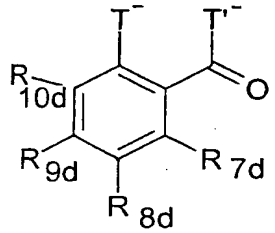


(V)

(II) to (X):



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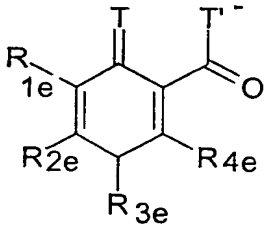

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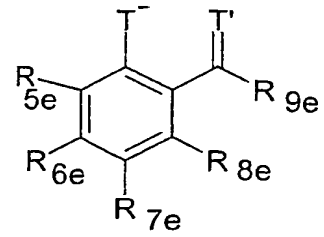

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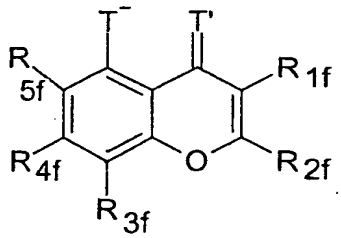

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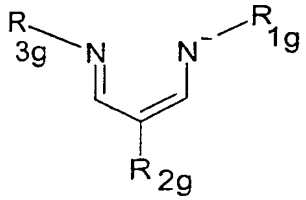


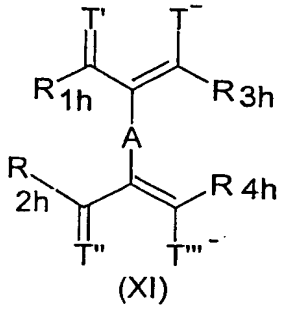
(X)

wherein T and T' are independently selected from O and S,

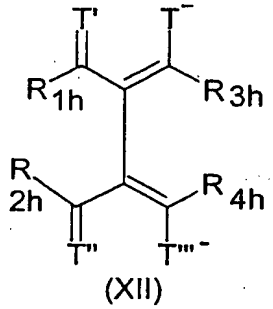
R_{1g} and R_{3g} are independently H, (C_1-C_6)alkyl, aryl or aralkyl,

R_{1c} to R_{5f} (i.e., R_{1c}, R_{2c}, R_{3c}, R_{4c}, R_{5c}, R_{6c}, R_{7c}, R_{8c}, R_{9c}, R_{1d}, R_{2d}, R_{3d}, R_{4d}, R_{5d}, R_{6d}, R_{7d}, R_{8d}, R_{9d}, R_{10d}, R_{1e}, R_{2e}, R_{3e}, R_{4e}, R_{5e}, R_{6e}, R_{7e}, R_{8e}, R_{9e}, R_{1f}, R_{2f}, R_{3f}, R_{4f} and R_{5f}) and R_{2g} are independently H, (C_1-C_6)alkyl, aryl, aralkyl, wherein the latter two groups are optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, SO_2N $R^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ and (C_1-C_6)alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and R^{15b} are independently selected from H, (C_1-C_6)alkyl, aryl or aralkyl.

The compounds of formula (I) may be in the form of dimers, which may also be termed dinuclear complexes – such complexes contain two ruthenium atoms. Dinuclear complexes can be provided by employing a ligand which comprises two linked ligands Y-L-Y' so as to bridge between two ruthenium centres. Therefore, in another embodiment of the invention, Y-L-Y' may be selected from ligands of formulae (XI) to (XV):



(XI)



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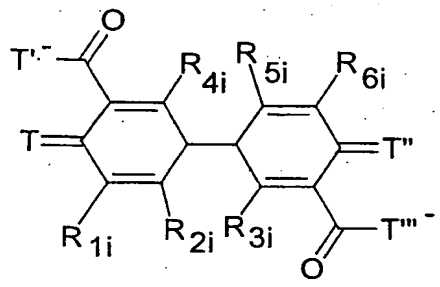

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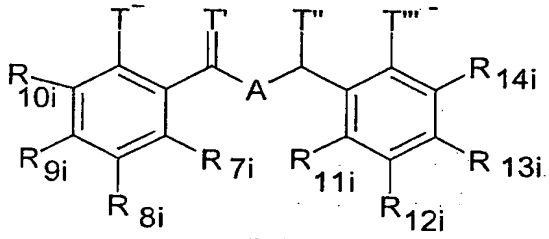

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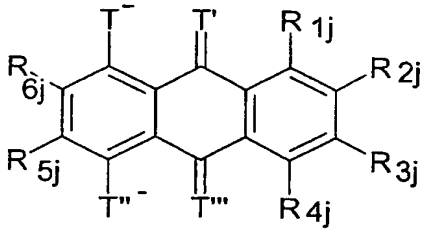


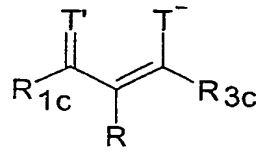
(XV)

wherein T, T', T'' and T''' are independently selected from O and S,

A comprises one or more groups selected from (C_1-C_6)alkylene, (C_1-C_6)alkenylene, (C_1-C_6)alkynylene, arylene, aralkylene, alkarylene, ferrocenylene, Se, Se-Se, S-S, N=N and C=O,

and R_{1h} to R_{6j} (i.e., R_{1h}, R_{2h}, R_{3h}, R_{4h}, R_{1i}, R_{2i}, R_{3i}, R_{4i}, R_{5i}, R_{6i}, R_{7i}, R_{8i}, R_{9i}, R_{10i}, R_{11i}, R_{12i}, R_{13i}, R_{14i}, R_{1j}, R_{2j}, R_{3j}, R_{4j}, R_{5j}, and R_{6j}) are independently H, (C_1-C_6)alkyl, aryl, aralkyl, wherein the latter two groups are optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, SO_2N $R^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ and (C_1-C_6)alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and $R^{15b}$are independently selected from H, (C_1-C_6)alkyl, aryl or aralkyl.

Particularly preferred compounds of formula (I) are those in which Y-L-Y' is:



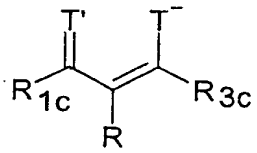
wherein T and T' are independently O and S, and

R, R_{1c} and R_{3c} are independently H, (C_1-C_6)alkyl, aryl, aralkyl, wherein the latter two groups are optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, SO_2N $R^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ and (C_1-C_6)alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and $R^{15b}$are as defined above. Even more preferably, T and T' are both O and R, R_{1c} and R_{3c} are independently (C_1-C_6)alkyl or phenyl, said phenyl optionally substituted by (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-

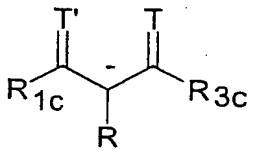
C_6)alkyl, halo, carboxyl, $CO_2(C_1$-$C_6)$alkyl, $CONH_2$, COH, $CO(C_1$-$C_6)$alkyl, SO_3H, SO_2NH_2, phenoxy, $(C_1$-$C_6)$alkylthio, NH_2 or $(C_1$-$C_6)$alkoxy. Most preferably, R is H or $(C_1$-$C_6)$alkyl and R_{1c} and R_{3c} are independently unsubstituted $(C_1$-$C_6)$alkyl or optionally substituted phenyl.

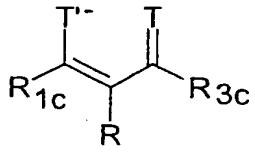
In the compounds of the invention, it is preferred that Y and Y' (including T, T', T'' and T''' in the above formulae) are all O.

Compounds of formula (I) and ligands of formula Y-L-Y' may exist in one or more tautomeric forms, all of which are covered by the present invention. For example, ligands of formula:



may have the following tautomeric forms:

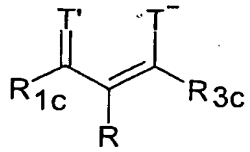




The existence and nature of the tautomers will depend on the structure of Y-L-Y'.

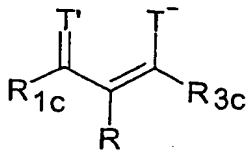
A particularly preferred group of compounds of formula (I) are those in which:
X is halo (preferably chloro);
R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from H, $(C_1$-$C_6)$alkyl and phenyl or R^1 and R^2 together with the ring to which they are bound represent anthracene or a hydrogenated derivative of anthracene, said phenyl and

anthracene or a hydrogenated derivative of anthracene group being optionally substituted by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, phenyl, benzyl, halo, carboxyl, $CO_2(C_1$-$C_6)$alkyl, $CONH_2$, COH, $CO(C_1$-$C_6)$alkyl, SO_3H, SO_2NH_2, phenoxy, $(C_1$-$C_6)$alkylthio, NH_2 or $(C_1$-$C_6)$alkoxy;
Y-L-Y' is:



wherein T and T' are both O, R is H or $(C_1$-$C_6)$alkyl and R_{1c} and R_{3c} are independently $(C_1$-$C_6)$alkyl or phenyl, said phenyl optionally substituted by from one to three groups selected from $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, halo, carboxyl, $CO_2(C_1$-$C_6)$alkyl, $CONH_2$, COH, $CO(C_1$-$C_6)$alkyl, SO_3H, SO_2NH_2, phenoxy, $(C_1$-$C_6)$alkylthio, NH_2 or $(C_1$-$C_6)$alkoxy.

A further preferred group of compounds of formula (I) is that in which:
R^1, R^2, R^3, R^4, R^5 and R^6 are all H, or one of R^1, R^2, R^3, R^4, R^5 and R^6 is phenyl and the other groups are all H, or one or two of R^1, R^2, R^3, R^4, R^5 and R^6 is or are $(C_1$-$C_6)$alkyl and the other groups are all H, or R^1 and R^2 together with the ring to which they are bound represent anthracene or a hydrogenated derivative of anthracene;
X is chloro; and
Y-L-Y' is:



wherein T and T' are both O, R is H and R_{1c} and R_{3c} are independently $(C_1$-$C_6)$alkyl or R_{1c} and R_{3c} are independently unsubstituted $(C_1$-$C_6)$alkyl or optionally substituted phenyl.

The compounds of the invention have been found to exhibit cytotoxic activity against cancer cell lines and can therefore be expected to show anticancer activity. The compounds may be used to kill cells *in vivo* or *ex vivo*.

In another embodiment, therefore, the present invention provides a compound of formula (I) as defined above without the provisos for use in medicine. The invention also contemplates the provision of a compound of formula (I) as defined above without the provisos for use in the treatment and/or prevention of cancer and the use of a compound of formula (I) as defined above without the provisos in the treatment and/or prevention of cancer.

Also provided by the invention is the use of a compound of formula (I) as defined above without the provisos in the manufacture of a medicament for the treatment and/or prevention of cancer.

Further provided by the invention is a pharmaceutical composition comprising a compound of formula (I) according as defined above without the provisos together with one or more pharmaceutically acceptable excipients.

Yet another aspect of the invention is a method of treating and/or preventing cancer which comprises administering to a subject a therapeutically effective amount of a compound of formula (I) as defined above without the provisos or a composition of the invention.

The compounds of the invention may be used directly against a tumour. Alternatively or additionally, the compounds may be used to prevent or inhibit metastasis and/or to kill secondary tumours. It will be understood that the prevention or inhibition of metastasis is encompassed by the term "preventing cancer", as used herein.

The term tumour includes all forms of neoplastic cell growth, including tumours of the lung, liver, blood cells, skin, pancreas, stomach, colon, prostate, uterus, breast, lymph glands and bladder. Ovarian tumours may be especially suitable for treatment according to the invention.

Compounds of the invention may be effective in treating and/or preventing tumours caused by cells that are resistant to other cytotoxic drugs, such as cis-platin, for example.

Certain compounds of the invention have the surprising advantage that they do not bind selectively to guanine bases but show roughly equal affinity for binding to guanine and adenine. This effect was unexpected, given that the presence of an N-H group available for hydrogen bonding was thought to be a requirement for bonding to guanine. Furthermore, binding to guanine and adenine gives the compounds a potentially greater ability to be less susceptible to drug resistance in tumour cells. In one embodiment, the compounds can be used in a method of binding non-selectively to guanine bases, preferably a method of binding to guanine and adenine bases with roughly equal affinity. This method may be, for example, a method of killing cells in vivo or ex vivo,

or another method such as the separation of guanine and adenine bases from a mixture.

The invention also provides a pharmaceutical composition comprising one or more compounds of the invention together with one or more pharmaceutically acceptable excipients. Suitable excipients include diluents and/or carriers.

The compounds of the invention may be administered by a number of routes including, for example, orally, parenterally (eg, by injection intramuscularly, intravenously or subcutaneously), topically, nasally or via slow releasing microcarriers. Thus, suitable excipients for use in the pharmaceutical compositions of the invention include saline, sterile water, creams, ointments, solutions, gels, pastes, emulsions, lotions, oils, solid carriers and aerosols.

The compositions of the invention may be formulated in unit or sub-unit dosage form including, for example, tablets, capsules and lozenges and containers containing the composition in a form suitable for parenteral administration. Preferably, the compositions are in a form that is suitable for injection.

The specific dosage level of the compounds and compositions of the invention will depend upon a number of factors, including the biological activity of the specific compound used and the age, body weight and sex of the subject. It will be appreciated that the subject may be a human or a mammalian animal.

The compounds and compositions of the invention can be administered alone or in combination with other compounds. The other compounds may have a biological activity which complements the activity of the compounds of the invention eg, by enhancing its effect in killing tumours or by reducing any side-effects associated with the compounds of the invention.

In another embodiment, the present invention provides a process for preparing the compound of formula (I) which comprises the reaction of a compound of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$, optionally in the form of a dimer, with Y-L-Y', in a suitable solvent for the reaction, wherein R^1,R^2, R^3, R^4, R^5, R^6, X, Y,Y' and L are as defined for formula (I) above. Preferably, the process comprises the reaction of a compound of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$, optionally in the form of a dimer, with a salt comprising Y-L-Y' as an anion (eg, a salt of an alkali metal such as sodium) at a temperature of from 0°C to 100°C (eg, 10°C to 50 °C) in a polar solvent such as a di(C_1-C_6)alkyl ketone (eg, acetone) or water or mixtures thereof. The compound of formula (I) can be separated from the reaction mixture, for example by extraction into a less polar solvent (eg, dichloromethane) and, optionally, purified (eg, by recrystallisation from a suitable solvent or mixture of two or more different solvents).

Suitable compounds of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$ for use as starting materials (starting ruthenium complexes) in the process of the invention can be produced as described in WO 01/30790 and WO 02/02572. Compounds of formula Y-L-Y' are either commercially available or can be synthesised by routes well known to those skilled in the art.

The invention will now be described with reference to the following non-limiting examples.

Examples

A. Synthesis

Example 1

[(η^6-*p*-cymene)RuCl($H_3CCOCHCOCH_3$ – *O,O*)].

The compound of Example 1 was prepared using the method described by D. Carmona et al, *J. Chem. Soc., Dalton Trans.*, 1990, 1463 – 1476.

[(η^6-*p*-cymene)$RuCl_2$]$_2$ (250 mg, 0.41 mmol) and sodium acetylacetonate monohydrate (150 mg, 1.07 mmol) were stirred in acetone (25 ml) at room temperature (RT) for 50 min. The extraction step then involved removal of the solvent *in vacuo* on a rotary evaporator, extraction of the product with dichloromethane, filtration using Whatman No. 541 filter paper, followed by removal of the solvent again on a rotary evaporator. The final product was recrystallised from acetone/diethyl ether and left in a freezer at 253 K overnight. The red crystals (180 mg, 0.48 mmol, 59% yield) were collected and dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 5.43 (d, 2H), 5.18 (d, 2H), 5.13 (s, 1H), 2.85 (sp, 1H), 2.24 (s, 3H), 1.97 (s, 6H), 1.30 (d, 6H).

Example 2

[(η^6-*p*-cymene)RuCl($F_3CCOCHCOCF_3$ – *O,O*)]

[(η^6-*p*-cymene)$RuCl_2$]$_2$ (250 mg, 0.41 mmol) and sodium hexafluoroacetylacetonate (260 mg, 1.13 mmol) were stirred in acetone (25 ml) at RT for 40 min. After the extraction step using dichloromethane (see Example 1), the final product was dissolved in diethyl ether, the solution was concentrated on a rotary evaporator, and hexane was added. The vessel was left in a freezer at 253K overnight. The crystals (277 mg, 0.58 mmol, 70.7% yield) were collected and dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 5.86 (s, 1H), 5.63 (d, 2H), 5.36 (d, 2H), 2.88 (sp, 1H), 2.24 (s, 3H), 1.33 (d, 6H).

Example 3

[(η^6-*p*-cymene)RuCl($C_6H_5COCHCOC_6H_5$ – *O,O*)]

1,3-diphenyl-1,3-propanedione (277 mg, 1.24 mmol) and sodium methoxide (62 mg, 1.15 mmol) were stirred in methanol (30 ml) at room temperature (RT) for 100 min. The solvent was removed *in vacuo* and the product was washed with diethyl ether, which was then removed *in vacuo* on a rotary evaporator. This sodium salt (210 mg, 0.85 mmol, 73.9% yield) and [(η^6-*p*-cymene)$RuCl_2$]$_2$ (240 mg, 0.39 mmol) were stirred in acetone (25 ml) at RT for 40 min. After the extraction step using dichloromethane (see Example 1), the final product was dissolved in acetone, concentrated on a rotary evaporator, and diethyl ether was added. The solution was left in a freezer at 253 K overnight. The crystals (238 mg, 0.48 mmol, 61.8% yield) were collected and dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 7.88 (m, 2H), 7.43 (m, 2H), 7.36 (m, 2H), 6.43 (s, 1H), 5.57 (d, 2H), 5.30 (d, 2H), 3.01 (sp, 1H), 2.33 (s, 3H), 1.39 (d, 6H).

Example 4

[(η^6-*p*-cymene)RuCl($(CH_3)_3CCOCHCOC(CH_3)_3$ – *O,O*)]

2,2,6,6-tetramethyl-3,5-heptanedione (299 mg, 1.62 mmol) and sodium methoxide (68 mg, 1.26 mmol) were stirred in methanol (40 ml) at RT for 5 h. The solvent and the excess liquid starting material were removed *in vacuo* on a rotary evaporator. The obtained sodium salt (233 mg, 1.13 mmol, 89.6% yield) and [(η^6-*p*-cymene)$RuCl_2$]$_2$ (258 mg, 0.42 mmol) were stirred in acetone (25 ml) at RT for 40 min. After the extraction step using dichloromethane (see Example 1), the residue was dissolved in diethyl ether, concentrated on a rotary evaporator, and hexane was added. The solution was left in a freezer at 253 K overnight. The crystals (215 mg, 0.47 mmol, 56.0 % yield) were collected and

dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 5.38 (d, 2H), 5.37 (s, 1H), 5.10 (d, 2H), 2.88 (sp, 1H), 2.21 (s, 3H), 1.33 (d, 6H), 1.10 (s, 18H).

Example 5

$[(\eta^6\text{-}C_6H_5C_6H_5)RuCl(H_3CCOCHCOCH_3 - O,O)]$

$[(\eta^6\text{-}C_6H_5C_6H_5)RuCl_2]_2$ (250 mg, 0.38 mmol) was refluxed in water (25 ml) for 2 h. The heat was reduced below boiling point and sodium acetylacetonate monohydrate (141 mg, 1.01 mmol) was added. The solution was stirred for 30 min and hot filtered. The solvent was removed *in vacuo* on a rotary evaporator. After the extraction step using dichloromethane (see Example 1), the residue was dissolved in little acetone, and diethyl ether was added until precipitation occurred. The vessel was left in a freezer at 253 K for 6 d. The product (65 mg, 0.16 mmol, 21.3% yield) was collected and dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 7.67 (m, 2H), 7.45 (m, 3H), 5.83 (m, 2H), 5.75 (m, 3H), 5.10 (s, 1H), 1.83 (s, 6H).

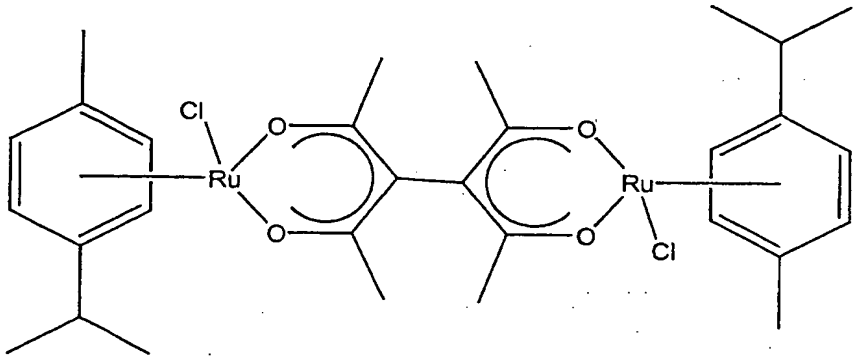
Example 6

$[(\eta^6\text{-}p\text{-cymene})Ru(CH_3CN)(H_3CCOCHCOCH_3 - O,O)]BF_4$

The compound of Example 1 (144 mg, 0.39 mmol) and $AgBF_4$ (72 mg, 0.37 mmol) were stirred in acetonitrile (20 ml) overnight. The resulting solution was filtered through glass wool and the solvent was removed *in vacuo* on a rotary evaporator. The residue was dissolved in a minimum amount of acetone, and diethyl ether was added until precipitation occurred. The flask was placed in a freezer at 253 K for 4 d. The crystals (149 mg, 0.32 mmol, 87.1% yield) were collected and dried *in vacuo*. ^{1}H NMR ($CDCl_3$): δ 5.74 (d, 2H), 5.48 (d, 2H), 5.16 (s, 1H), 2.85 (sp, 1H), 2.43 (s, 3H), 2.21 (s, 3H), 1.98 (s, 6H), 1.33 (d, 6H).

Example 7

[(η^6-*p*-cymene)RuCl($H_3CCOCCOCH_3$ – *O,O*)]$_2$



The preparation of the tetradentate ligand tetraacetylethane has been reported by Robert. G. Charles in *Organic Syntheses* (1959), *39*, 61. Tetraacetylethane (208 mg, 1.05 mmol) was reacted in water with 21 ml of a 0.1 M solution of KOH in methanol for 2 h. The solvents were evaporated and the salt was dissolved in acetone. [(*p*-Cymene)$RuCl_2$]$_2$ (643 mg, 1.05 mmol) was added to the solution and the mixture was reacted for 3 h. The solvent was evaporated and the residue was extracted with CH_2Cl_2. Filtration and evaporation of the solvent gave the pure dinuclear complex, which was recrystallized from acetone (550 mg, 71%).

B. Biological Data

1. Protocol for testing Ru compounds

The compounds are tested on 24-well trays. Cells growing in a flask are harvested just before they become confluent, counted using a haemocytometer and diluted down with media to a concentration of $1x10^4$ cells per ml. The cells are then seeded in the 24-well trays at a density of $1x10^4$ cells per well (i.e. 1ml of the diluted cell suspension is added to each well). The cells are then left to

plate down and grow for 72 hours before adding the compounds of the invention.

The Ru complexes are weighed out and made up to a concentration of 1mg/ml with deionised water and 0.5 % w/w DMSO. The appropriate volume of the Ru solution is added to 5ml of media to make it up to a concentration of 100 μM for each drug. This 100 μM solution is then serially diluted to make up the 10 μM, 1 μM and 0.1 μM solutions.

The media is removed from the cells and replaced with 1ml of the media dosed with drug. Each concentration is done in duplicate. A set of control wells are left on each plate, containing media and 0.5 % w/w DMSO without drug.

The cells are left exposed to the drugs for 24 hours and then washed with phosphate buffered saline before fresh media is added.

They are allowed to grow on for a further 3 days before being counted using a Coulter counter.

Preparing cells for counting:

Media is removed and 1ml of PBS is added to the cells.
250 μl of trypsin is added and cells left in incubator for a few minutes to allow the monolayers to detach.
Once trypsinised, 250μl of media is added to each well to neutralise the trypsin.
200μl of this suspension is added to 10ml of NaCl for counting.

2. Results

Using the above protocol, a number of compounds of the invention were tested on A2780 ovarian cancer cell line. Compounds of the invention have an IC50 of less than 150 μM, preferably less than 100 μM, more preferably less than 50 μM when tested according to this protocol. The results are as follows:

Compound (Example No.)	IC50 (μM)
1	19
2	>100
3	11
4	14
5	21
6	22
7	-

C. NMR Data

The ability of the compounds of the invention to bind to DNA bases was studied by nmr and the results are illustrated in the accompanying figures in which:

Figure 1 is a 500 MHz ^{1}H NMR spectrum of a mixture of guanosine : adenosine : compound of Example 1 in the mole ratio 1.3 : 1 : 1, respectively, in 10% D_2O/90% H_2O.

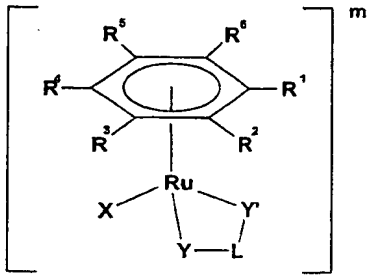
Figure 2 shows expansions of the regions 5.1-5.4 ppm and 7.9-8.6 ppm of the ^{1}H NMR spectrum shown in Fig.1.

In Figure 2, the region from 5.1 to 5.4 ppm (right) corresponds to the central CH on the acac ligand. Peaks a and b correspond to the adenosine adducts,

peak c to the guanosine adduct. In the region 7.9- 8.6 ppm (left), peaks for the H2 and H8 protons of adenosine and H8 protons of guanosine appear. It can be seen that both adenosine and guanosine form adducts with the compound of Example 1 (bound labels). The atom labelling scheme for the nucleobase part (A and G) of the nucleosides is shown.

CLAIMS

1. Ruthenium(II) compound of formula (I):



(I)

wherein: R^1, R^2, R^3, R^4, R^5 and R^6 independently represent H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, halo, CO_2R^7, $CONR^8R^9$, COR^{10}, SO_3H, $SO_2N\ R^{11}R^{12}$, aryloxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-N=N-R^{13}$, $NR^{14}R^{15}$, aryl or aralkyl, which latter two groups are optionally substituted on the aromatic ring by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aryl, aralkyl, halo, CO_2R^{7a}, $CONR^{8a}R^{9a}$, COR^{10a}, SO_3G, $SO_2NR^{11a}R^{12a}$, aryloxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-N=N-R^{13a}$, $NR^{14a}R^{15a}$, or R^1 and R^2 together with the ring to which they are bound represent a saturated or unsaturated carbocyclic or heterocyclic group containing up to three 3- to 8- membered carbocyclic or heterocyclic rings, wherein each carbocyclic or heterocyclic ring may be fused to one or more other carbocyclic or heterocyclic rings, and wherein each of the rings may be optionally substituted by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aryl, aralkyl, halo, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3G, $SO_2NR^{11b}R^{12b}$, aryloxy, $(C_1$-$C_6)$alkylthio, $-N=N-R^{13b}$, $NR^{14b}R^{15b}$ or $(C_1$-$C_6)$alkoxy;

R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{14a}, R^{15a}, R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and R^{15b} are independently selected from H, (C_1-C_6)alkyl, aryl or aralkyl;

X is a neutral or negatively charged O-, N- or S- donor ligand or halo;

G and G' are independently selected from alkali metals, aryl, aralkyl and (C_1-C_6) alkyl;

Y-L-Y' is a bidentate ligand bearing a negative charge with a proportion of the charge on both Y and Y', Y and Y' are independently selected from O, S or NR^{16}, wherein R^{16} is H, (C_1-C_6)alkyl, aryl or aralkyl, and L is a group linking Y and Y' and comprises one or more groups selected from (C_1-C_6)alkylene, (C_1-C_6)alkenylene, (C_1-C_6)alkynylene, arylene, aralkylene, alkarylene, each of said latter six groups being optionally substituted, ferrocenylene, Se, Se-Se, S-S, N=N and C=O;

m is −1, 0 or +1 and the compound comprises a counterion when m is −1 or +1;

the compound of formula (I) optionally being in the form of a dimer in which two L groups are linked either directly or through a group comprising one or more of (C_1-C_6)alkylene, (C_1-C_6)alkenylene, arylene, aralkylene, alkarylene, Se, Se-Se, S-S, N=N and C=O or in which L bears two Y groups and two Y' groups;

with the proviso that:

when Y-L-Y' is $(CH_3C(O)CHC(O)CH_3)^-$, X is halo or an N-donor ligand, R^1, R^2, R^3, R^4, R^5 and R^6 together with the ring to which they are bound do not represent 4-isopropyl-1-methylbenzene;

when Y-L-Y' is $(CH_3C(O)CHC(O)CH_3)^-$ and X is chloro, $(CH_3)_2SO$, CH_3CN, pyridine or $(CH_3C(O)CHC(O)CH_3)^-$: R^1, R^2, R^3, R^4, R^5 and R^6 are not all H or all methyl; R^1, R^3 and R^5 are not all H when R^2, R^4 and R^6 are all methyl; and R^2, R^4 and R^6 are not all H when R^1, R^3 and R^5 are all methyl; and

when Y-L-Y' is $(CF_3C(O)CHC(O)CF_3)^-$ and X is chloro, R^1, R^2, R^3, R^4, R^5 and R^6 are not all H or all methyl; R^1, R^3 and R^5 are not all H when R^2, R^4 and R^6

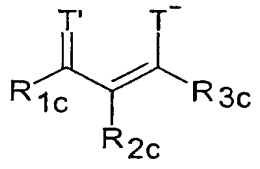
are all methyl; and R^2, R^4 and R^6 are not all H when R^1, R^3 and R^5 are all methyl.

2. Compound as claimed in Claim 1, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from H, $(C_1$-$C_6)$alkyl and phenyl or R^1 and R^2 together with the ring to which they are bound represent anthracene or a hydrogenated derivative of anthracene, said phenyl and anthracene or a hydrogenated derivative of anthracene group being optionally substituted by one or more groups independently selected from $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, hydroxy$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, phenyl, benzyl, halo, carboxyl, $CO_2(C_1$-$C_6)$alkyl, $CONH_2$, COH, $CO(C_1$-$C_6)$alkyl, SO_3H, SO_2NH_2, phenoxy, $(C_1$-$C_6)$alkylthio, NH_2 or $(C_1$-$C_6)$alkoxy.

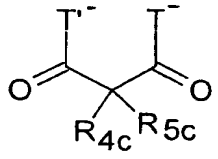
3. Compound as claimed in Claim 1 or Claim 2, wherein m is 0.

4. Compound as claimed in any one of Claims 1 to 3, wherein X is halo or CH_3CN.

5. Compound as claimed in any one of Claims 1 to 4, wherein Y-L-Y' is selected from ligands of formulae (II) to (X):



(II)



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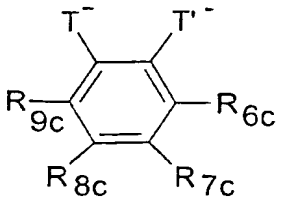
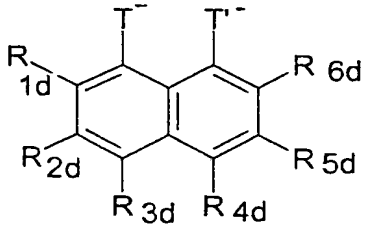
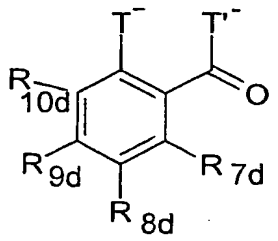


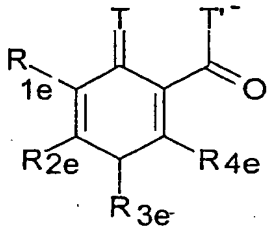
(IV)



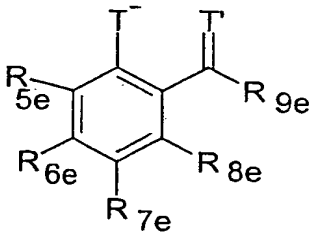
(V)



(VI)



(VII)



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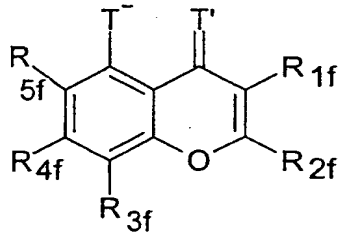

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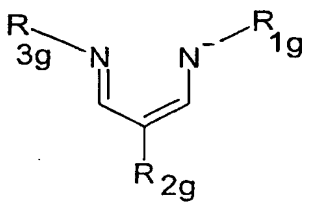


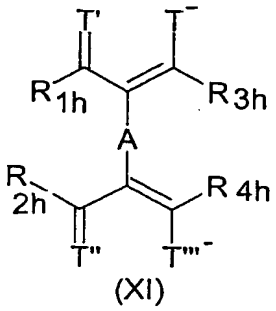
(X)

wherein T and T' are independently selected from O and S,

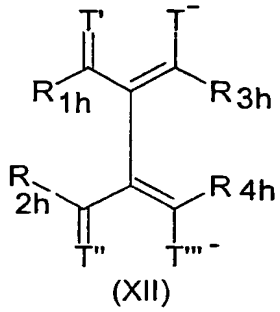
R_{1g} and R_{3g} are independently H, $(C_1\text{-}C_6)$alkyl, aryl or aralkyl,

R_{1c} to R_{5f} and R_{2g} are independently H, $(C_1\text{-}C_6)$alkyl, aryl, aralkyl, wherein the latter two groups and the corresponding groups for R_{1g} and R_{3g} are optionally substituted by one or more groups independently selected from $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, $SO_2N\ R^{11b}R^{12b}$, aryloxy, $(C_1\text{-}C_6)$alkylthio, $-N{=}N\text{-}R^{13b}$, $NR^{14b}R^{15b}$ and $(C_1\text{-}C_6)$alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and R^{15b} are as defined in Claim 1.

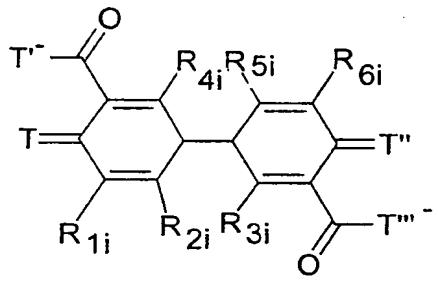
6. Compound as claimed in any one of Claims 1 to 4, wherein Y-L-Y' is selected from:



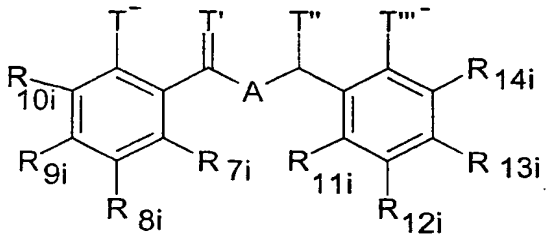
(XI)



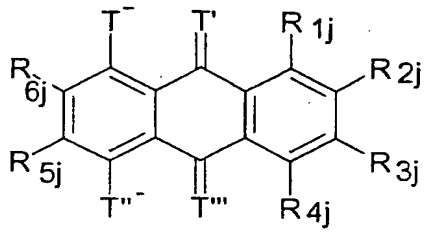
(XII)



(XIII)



(XIV)



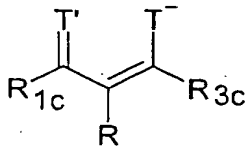
(XV)

wherein T, T', T'' and T''' are independently selected from O and S,

A comprises one or more groups selected from (C_1-C_6)alkylene, (C_1-C_6)alkenylene, (C_1-C_6)alkynylene, arylene, aralkylene, alkarylene, ferrocenylene, Se, Se-Se, S-S, N=N and C=O

and R_{1h} to R_{6j} are independently H, (C_1-C_6)alkyl, aryl, aralkyl, wherein the latter two groups are optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, $SO_2N\ R^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ and (C_1-C_6)alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and $R^{15b}$are as defined in Claim 1.

7. Compound as claimed in any one of Claims 1 to 4, wherein Y-L-Y' is:



wherein T and T' are independently O and S, and

R, R_{1c} and R_{3c} are independently H, (C_1-C_6)alkyl, aryl, aralkyl, wherein the latter two groups are optionally substituted by one or more groups independently selected from (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl, aralkyl, halo, carboxyl, CO_2R^{7b}, $CONR^{8b}R^{9b}$, COR^{10b}, SO_3H, $SO_2N\ R^{11b}R^{12b}$, aryloxy, (C_1-C_6)alkylthio, -N=N-R^{13b}, $NR^{14b}R^{15b}$ and (C_1-C_6)alkoxy, wherein R^{7b}, R^{8b}, R^{9b}, R^{10b}, R^{11b}, R^{12b}, R^{13b}, R^{14b} and $R^{15b}$are as defined in Claim 1.

8. Compound as claimed in Claim 7, wherein T and T' are both O, R is H or $(C_1\text{-}C_6)$alkyl and R_{1c} and R_{3c} are independently $(C_1\text{-}C_6)$alkyl or phenyl, said phenyl optionally substituted by $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, halo, carboxyl, $CO_2(C_1\text{-}C_6)$alkyl, $CONH_2$, COH, $CO(C_1\text{-}C_6)$alkyl, SO_3H, SO_2NH_2, phenoxy, $(C_1\text{-}C_6)$alkylthio, NH_2 or $(C_1\text{-}C_6)$alkoxy.

9. Compound as claimed in claim 8, wherein R is H and R_{1c} and R_{3c} are independently $(C_1\text{-}C_6)$alkyl or phenyl.

10. Compound as claimed in any one of Claims 1 to 9, wherein Y and Y' are both O.

11. Compound of formula (I) according to any one of Claims 1 to 10 without the provisos, for use in medicine.

12. Use of a compound of formula (I) according to any one of Claims 1 to 10 without the provisos, in the manufacture of a medicament for the treatment and/or prevention of cancer.

13. Pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 10 without the provisos, together with one or more pharmaceutically acceptable excipients.

14. A method of treating and/or preventing cancer which comprises administering to a subject a therapeutically effective amount of a compound of formula (I) according to any one of Claims 1 to 10 without the provisos, or a composition of Claim 13.

15. Process for preparing the compound of any one of Claims 1 to 10 which comprises the reaction of a compound of formula $[(\eta^6\text{-}C_6(R^1)(R^2)(R^3)(R^4)(R^5)(R^6))RuX_2]$, optionally in the form of a dimer, with Y-L-Y, in a suitable solvent for the reaction, wherein R^1,R^2, R^3, R^4, R^5, R^6, X, Y,Y' and L are as defined in Claim 1.

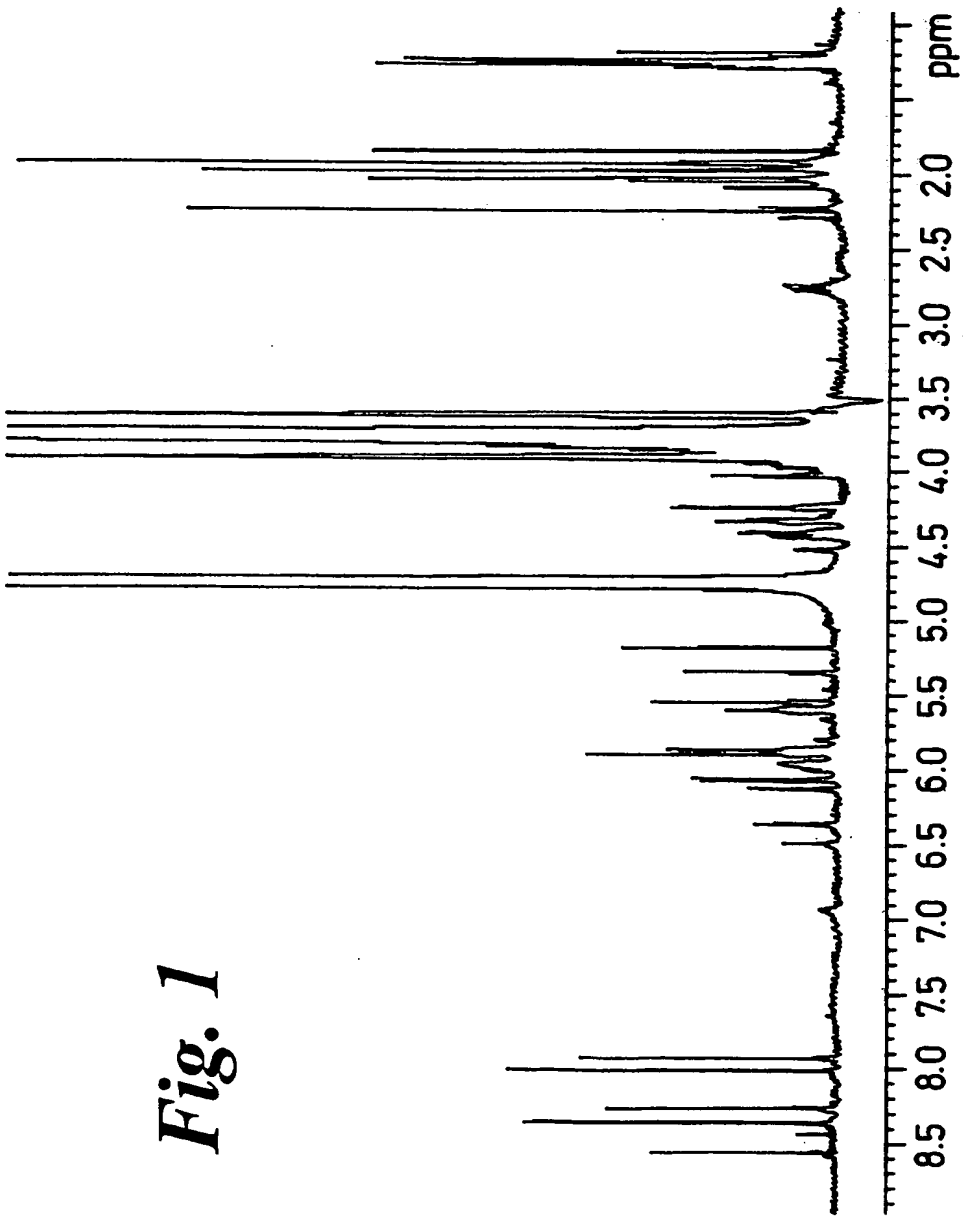


Fig. 1

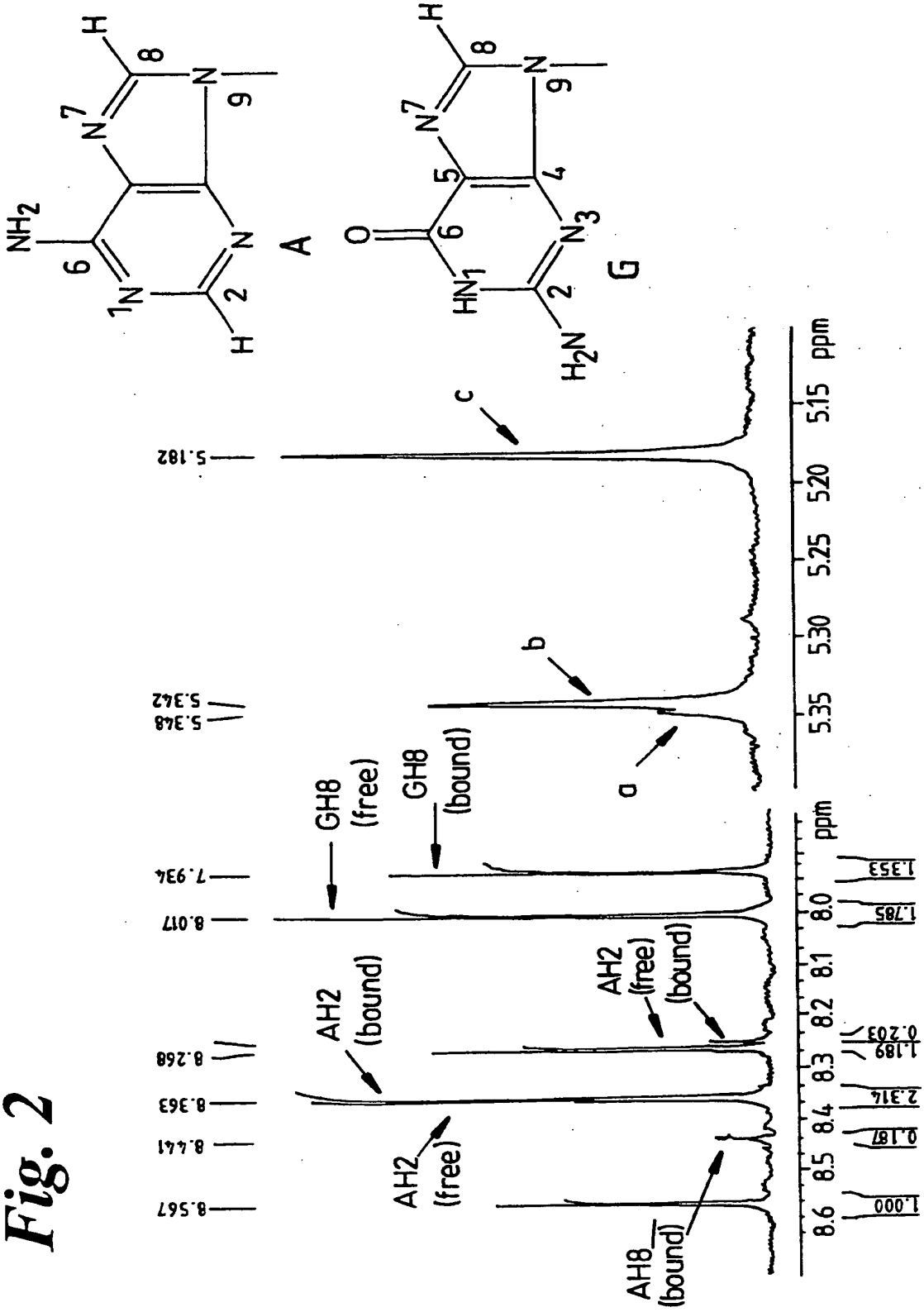

A
G
c
b
a
GH8 (free)
GH8 (bound)
AH2 (bound)
AH2 (free)
AH2 (free) (bound)
AH8 (bound)
5.182
5.348
5.342
7.934
8.017
8.268
8.363
8.441
8.567
ppm
5.15
5.20
5.25
5.30
5.35
8.0
8.1
8.2
8.3
8.4
8.5
8.6
1.353
1.785
0.203
1.189
2.314
0.187
1.000

Fig. 2

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 03/02879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SHIN, RICHARD Y. C. ET AL: "Arene-Ruthenium Complexes of an Acyclic Thiolate-Thioether and Tridentate Thioether Derivatives Resulting from Ring-Closure Reactions" INORGANIC CHEMISTRY (2003), 42(1), 96-106 , XP002259899 schemes 1-5 table 1 --- -/--	1-3,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2003	17/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.E. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Richter, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BEN AMMAR, HAMED ET AL: "Synthesis of bis-oxazoline-ruthenium(II)-arene complexes. Combined catalytic isomerization and Claisen rearrangement of bis-allyl ether" JOURNAL OF ORGANOMETALLIC CHEMISTRY (2002), 662(1-2), 63-69 , XP002259901 the whole document ---	1-4,15
X	CHEN HAIMEI ET AL: "Organometallic ruthenium(II) diamine anticancer complexes: arene-nucleobase stacking and stereospecific hydrogen-bonding in guanine adducts." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. UNITED STATES 27 MAR 2002, vol. 124, no. 12, 27 March 2002 (2002-03-27), pages 3064-3082, XP002259900 ISSN: 0002-7863 cited in the application the whole document ---	1-4, 11-15
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BELL, MICHAEL N. ET AL: "Carbocyclic complexes incorporating macrocyclic ligands. The synthesis and single crystal x-ray structure of the binuclear species dichlorobis(.eta.-pentamethylcyclopentadienyl)(1,4,7,10,13,16-hexathiacyclooctadecane)dirhodium bis(tetraphenylborate)" retrieved from STN Database accession no. 106:84806 XP002259903 abstract & JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS (1986), (6), 471-2 , --- -/--	1-3,15

INTERNATIONAL SEARCH REPORT

Int ıel Application No
PCT/GB 03/02879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BENNETT, MARTIN A. ET AL: "Mono- and bis-(acetylacetonato) complexes of arene-ruthenium(II) and arene-osmium(II): variation of the binding mode of.eta.1-acetylacetonate with the nature of the arene" retrieved from STN Database accession no. 135:371841 XP002259904 abstract & CANADIAN JOURNAL OF CHEMISTRY (2001), 79(5/6), 655-669 ,	1-4,15
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DAVIES, DAVID L. ET AL: "(Arene)ruthenium Complexes with Bis(oxazolines): Synthesis and Applications as Asymmetric Catalysts for Diels-Alder Reactions" retrieved from STN Database accession no. 135:152944 XP002259905 abstract & ORGANOMETALLICS (2001), 20(14), 3029-3034 ,	1-4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OHNISHI, TAKAFUMI ET AL: "Coordination behavior of ruthenium(II) complexes with alcohol ligand tethered to.eta.6-arene donor" retrieved from STN Database accession no. 131:257682 XP002259906 abstract & CHEMISTRY LETTERS (1999), (8), 809-810 ,	1-4,15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; EVERAERE, KATHELYNE ET AL: "(.beta.-Amino alcohol)(arene)ruthenium(II)-catalyzed asymmetric transfer hydrogenation of functionalized ketones - scope, isolation of the catalytic intermediates, and deactivation processes" retrieved from STN Database accession no. 134:295540 XP002259907 abstract & EUROPEAN JOURNAL OF ORGANIC CHEMISTRY (2001), (2), 275-291 , ---	1-4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WOISETSCHLAGER, OLIVER E. ET AL: "Hydrocarbon-bridged metal complexes. Part 49. Coordination chemistry of bis(ferrocenyl)-substituted 1,3-diketonates with ruthenium, rhodium, iridium, and palladium" retrieved from STN Database accession no. 132:308480 XP002259908 abstract & ZEITSCHRIFT FUER ANORGANISCHE UND ALLGEMEINE CHEMIE (2000), 626(3), 766-774 , ---	1-4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KATHO, AGNES ET AL: "Enantioselective hydride transfer hydrogenation of ketones catalyzed by '(.eta.6-p-cymene)Ru(amino acidato)Cl! and '(.eta.6-p-cymene)Ru(amino acidato)!3(BF4)3 complexes" retrieved from STN Database accession no. 132:222637 XP002259909 abstract & JOURNAL OF ORGANOMETALLIC CHEMISTRY (2000), 593-594, 299-306 , --- -/--	1-4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MIYAKI, Y. ET AL: "Synthesis and reaction of ruthenium(II) complexes containing heteroatom donor (O, N, and P) tethered to.eta.6-arene ring" retrieved from STN Database accession no. 133:135395 XP002259910 abstract & INORGANICA CHIMICA ACTA (2000), 300-302, 369-377 ,	1-4
X	FALLER, J. W. ET AL: "Highly enantioselective Diels-Alder catalysis with a chiral ruthenium bisoxazoline complex" JOURNAL OF ORGANOMETALLIC CHEMISTRY (2001), 630(1), 17-22 , XP002259902 scheme 3	1-4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SIMAL, FRANCOIS ET AL: "Ruthenium complexes containing diamine-based ligands as catalysts for insertion of carbenes into O-H bonds of alcohols" retrieved from STN Database accession no. 130:222808 XP002259911 abstract & TETRAHEDRON LETTERS (1999), 40(1), 63-66 ,	1-4,15
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUROSAWA, HIDEO ET AL: "Second sphere coordination behavior of aquo and amine ligands bound to a.eta.6-benzeneruthenium(II) cation" retrieved from STN Database accession no. 128:257553 XP002259912 abstract & INORGANICA CHIMICA ACTA (1998), 270(1,2), 87-94 ,	1-4,15

-/—

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUHLWEIN, FRANK ET AL: "Metal complexes of dyes. Part 9. Transition metal complexes of curcumin and derivatives" retrieved from STN Database accession no. 127:228818 XP002259913 abstract & ZEITSCHRIFT FUER ANORGANISCHE UND ALLGEMEINE CHEMIE (1997), 623(8), 1211-1219 ,	1-5
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KRAEMER, ROLAND ET AL: "Metal complexes of biologically important ligands. LIII. Chiral half-sandwich complexes of rhodium(III), iridium(III), iridium(I), and ruthenium(II) with.alpha.-amino acid anions" retrieved from STN Database accession no. 112:198744 XP002259914 abstract & CHEMISCHE BERICHTE (1990), 123(4), 767-78 ,	1-4,15
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHELDRICK, W. S. ET AL: "Synthesis and structural characterization of.eta.6-areneruthenium(II) complexes of.alpha.-amino acids with coordinating side chains" retrieved from STN Database accession no. 113:59793 XP002259915 abstract & JOURNAL OF ORGANOMETALLIC CHEMISTRY (1989), 377(2-3), 357-66 ,	1-4,15

-/--

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/GB 03/02879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GOETZE, H. J. ET AL: "Separation of amino-acidato ruthenium(II) complexes by ion-pair chromatography" retrieved from STN Database accession no. 120:94149 XP002259916 abstract & FRESENIUS' JOURNAL OF ANALYTICAL CHEMISTRY (1993), 346(6-9), 634-8 ,	1-4
A	EP 0 916 637 A (JAPAN SCIENCE AND TECHNOLOGY CORPORATION, JAPAN;NKK CORPORATION; TAKED) 19 May 1999 (1999-05-19) Compounds 10,11,14,15 example 71A; table 10	1-3,15
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CARMONA, DANIEL ET AL: "Heterobi- and Heterotetranuclear RuRh and RuIr Complexes with 2,2'-Biimidazolate and 2,2'-Bibenzimidazolate Anions as Bridging Ligands" retrieved from STN Database accession no. 122:214225 XP002259931 abstract & ORGANOMETALLICS (1995), 14(4), 2066-80 ,	1-4
A	STERN C ET AL: "The use of macrocyclic and polydentate ligands in ruthenium organometallic chemistry" JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 593-594, January 2000 (2000-01), pages 86-95, XP004185686 ISSN: 0022-328X scheme 1 figure 6	1,2

INTERNATIONAL SEARCH REPORT

Inte[illegible]al Application No
PC[illegible]B 03/02879

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0916637 A	19-05-1999	JP 2962668 B2	12-10-1999
		JP 9157196 A	17-06-1997
		JP 2912572 B2	28-06-1999
		JP 9157228 A	17-06-1997
		JP 3040353 B2	15-05-2000
		JP 10130289 A	19-05-1998
		EP 0916637 A1	19-05-1999
		US 6184381 B1	06-02-2001
		CA 2239970 A1	12-06-1997
		EP 1300381 A1	09-04-2003
		WO 9720789 A1	12-06-1997